Scenario/Driving questions	AD use case	Data source/search	PD use case	Data source/search
Scientist is working on immunotherapy as therapy for neurodegeneration. Wants to know what is the best target for AD and PD? Searches for hypotheses as a starting point.	Hypothesis: Amyloid beta (Abeta) is the pathogenic agent causing Alzheimer disease (AD). Reduction of Abeta will treat AD	*SWAN hypotheses* *Alzforum* Selkoe	Hypothesis: α-synuclein peptide is the toxic agent that causes Parkinson disease (PD). Reduction of α-synuclein will treat PD	*PubMed* Kruger et al., 2000 Lee & Trojanowski, 2006 Recchia et al., 2004 Mizuta et al., 2006
Each protein adapts multiple forms in disease. **Q: What Abeta and a-syn peptide assemblies have been reported?**	RS: Abeta forms monomer, dimer, trimer, ADDL (3 to 12-mer), 12-mer, protofibril, fibril	**SWAN**	**RS:Form filamentous assemblies or aggregations (beta sheets).**	*PubMed* Biocyc **Goedert et al. 2001**
Each protein exists in multiple cellular locations in disease.	RS: Abeta forms both extracellular deposits and intracellular inclusions	SWAN PubMed Marchesi Selkoe	RS: a-syn forms primarily intracellular inclusions (Lewy bodies), but may also be extracellular	Hashimoto et al., 2003
Q. What form of Abeta is the appropriate target? **Q. What form of a-syn is the appropriate target?**	RS: A novel form called Abeta*56 causes memory impairment in Tg2576 mouse model of AD	SWAN PubMed Lesne	RS: Lewy body-like fibrils and spherical assemblies are formed most rapidly by A53T, a mutation in the gene encoding alpha-synuclein linked to early-onset Parkinson's disease (PD)	PubMed Conway et al., 1998
Q. What are characteristics of Abeta*56? **Q. What are characteristics of pathogenic a-synuclein?**	RS: Abeta*56 weighs around 56 kilodaltons and is consistent with it being a 12-mer	SWAN PubMed Lesne	RS: While alpha-synuclein can form several different aggregate morphologies including oligomers, protofibrils and fibrils, the role of these morphologies in the progression of PD is not known.	PubMed Li et al., 2001 Spillantini et al., 1998
Q. Have similar forms of Abeta been reported by others?	RS: An ADDL is an Abeta-derived oligomers with dementing activity, with molecular composition of 3-24 monomeric subunits	SWAN PubMed		
Q. Is there data for	RS: *The prominent*	SWAN	RS: Cytoplasmic aggregates of a-	*PubMed* BIND?

existence of Abeta*56 in human AD? **Q. Is there data for existence of toxic synuclein assemblies in human PD?**	*immunoreactive species in soluble AD brain extracts thus was identified as an Abeta 12-mer*	PubMed Catalano et al., 2006 Lambert et al., 2007	synuclein have been visualized in neurons and glial cells as circular or coil-shape.	Biocyc, CCDB? Lashuel et al., 2002 Volles & Lansbury, 2002 Lee & Lee, 2002
	RS: Properties of ADDL in human AD are consistent with those of Abeta*56	Georganopoulou et al., 2005		
Q. How does Abeta*56 or ADDL impair memory or cause neuronal death? **Q. How does a-syn cause dysfunction of death of dopaminergic neurons?**	RS: ADDL impairs long-term potentiation (LTP)	SWAN PubMed Lacor et al., 2004 Gong et al., 2003	RS: Fibrillization of alpha-synuclein into protofibrils form pore-like assemblies on the surface of brain-derived vesicles. Cytosolic dopamine in dopaminergic neurons promotes the accumulation of toxic alpha-synuclein protofibrils.	Biocyc *PubMed* Zhang et al., 2005 Conway et al., 2001 Follmer et al., 2007 Mazzulli et al., 2006 Rochet et al., 2004 Serpell et al., 2000
Q. Is LTP present in parts of the brain affected by AD? **Q. Is LTP present in parts of the brain affected by PD?**	RS: LTP is exhibited by hippocampal CA1 neurons	Neuron DB	RS. LTP is observed in corticostriatal synapses.  Adobe Acrobat 7.0 Document	**Checked out NeuronDB for Neural Compartmental receptors having Nigral dopaminergic cell as Neuron blank needs to be populated**
Q. What parts of the brain are affected by AD? **Q. What parts of the brain are affected by PD?**	RS. Areas affected in early AD include: Hippocampal CA1, entorhinal cortex, basal forebrain cholinergic neurons	SWAN PubMed Apostolova et al., 2006	RS: Areas affected in early PD include: dorsal motor nucleus of the vagus, intermediate reticular zone, caudal raphe nuclei, locus ceruleus.	CCDB PubMed Baloyannis et al., 2006 Papapetropoulos, 2006 Shults, 2006

Q. What channels or receptors are involved in LTP?	RS: A- and D-type K channels are involved in LTP. "The experimental and modeling results support the hypothesis that dendritic K-A channels and the boosting of back-propagating action potentials contribute to the induction of LTP in CA1 neurons."	NeuronDB BrainPharm Watanabe et al., 2002	RS: D1 and D2 receptors are involved in LTP	NeuronDB BrainPharm
Q. Are A- or D-type K channels expressed in areas affected by AD? What about areas affected in PD?	RS: Hippocampal CA1 neurons express A-type K channels	Neuron DB CA1 pyramidal neuron/channels	RS: Neocortical layer V pyramidal neurons express A-type K channels.	PubMed Bekkers 2000
	RS: The A-type K current is reduced by Abeta	BrainPharm Plant et al., 2006		
Q. Would an antibody directed against ADDL / Abeta*56 restore A-current in the mouse model hippocampal neuron (e.g. in an organotypic slice prep)? **Q. Would an antibody directed against synuclein/aggregates restore A-current in the mouse model dopaminergic neuron (e.g. in an organotypic slice prep)?**	UNKNOWN: Future experiment?	PubMed BrainPharm	UNKNOWN: Future experiment?	PubMed BrainPharm
Q. What genes are expressed in both hippocampus and striatium; do any affect receptors or channel properties?		**The Allen Brain Atlas**		**CCDB**

Hypothesis: Immunization is a strategy to remove the toxic peptide and thereby prevent or treat AD and PD	RS: Immunization with synthetic Abeta peptide cleared plaques in the PDAPP mouse model	SWAN; PubMed Schenk et al., 1999 Maier et al., 2006 Klyubin et al., 2005 Hock et al., 2003	RS: Immunization with recombinant human alpha-synuclein reduced intracellular AS accumulation, preserved synaptic density.	PubMed Masliah et al., 2005 Pilcher, 2005
Q. Adverse effects associated with immunotherapy?	RS: The first clinical trial of an AD vaccine was halted because patients developed encephalitis.		Q: Are the safety issues raised in the AD trial of concern for a PD trial?	
Q: Why did some, but not all, patients, develop encephalitis?	RS: Interferon gamma may be involved in triggering encephalitis in some patients following Abeta immunization.	PubMed O'Toole et al., 2005 Monsonego et al., 2006		
Q: What genes are involved in Interferon gamma regulation?		Gene Network KEGG		
Q: What genes are activated following IfnG signalling?		Gene Network KEGG		
Q: Could any of the genes involved in IfnG signalling act as a biomarker with predictive value for encephalitis?		PubMed		
Q: Could a common immunotherapy treat both AD and PD?	Hypothesis: Both AD and PD represent pathologies induced by misfolded proteins adapting pathogenic conformations.	PubMed Walsh & Selkoe, 2004 Quist et al., 2005 Glabe, 2006	Hypothesis: Both AD and PD represent pathologies induced by misfolded proteins adapting pathogenic conformations.	PubMed Walsh & Selkoe, 2004 Quist et al., 2005 Glabe, 2006
Q. Is there evidence for a common antigen target in both AD and PD?	RS: Atomic force microscopy shows that Abeta forms channel-like structures induced by membranes.	PubMed Alzforum? SWAN?	RS: Atomic force microscopy shows that synuclein forms channel-like structures induced by membranes.	PubMed CCDB? Furukawa et al., 2006
Q: Are channels formed by aberrantly misfolded Abeta distinguishable from normally occurring pores		PubMed BrainPharm		PubMed CCDB? BrainPharm

or channels?				
Q: Can other proteins associated with neurodegenerative disease form pathogenic conformations in a similar manner to Abeta and a-synuclein?		PubMed BrainPharm		PubMed Thompson & Barrow, 2002 BrainPharm
Q: Could a common immunotherapy strategy targeting misfolded protein ion channels be useful in both AD and PD? Huntington Disease? Prion disease?		PubMed		PubMed Thompson & Barrow, 2002